CLINICAL USEFULNESS OF B-TYPE NATRIURETIC PEPTIDE MEASUREMENT: PRESENT AND FUTURE PERSPECTIVES

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The identification of natriuretic peptides led to an explosion of basic and clinical investigations to clarify their physiology, pathophysiologic role in heart failure, and clinical usefulness. The knowledge base and emerging information on B-type natriuretic peptide (BNP) is plentiful but the consensus on its application is still sparse.

The natriuretic peptide family comprises atrial natriuretic peptide (ANP), BNP, C-type natriuretic peptide (CNP), and D-type natriuretic peptide. ANP and BNP are synthesised in the heart, CNP is produced mainly in vessels, and D-type natriuretic peptide has been isolated in plasma and atrial myocardium.

The precursor prohormone of each natriuretic peptide is encoded by a separate gene. BNP is a 108 amino acid pro-hormone that, after cleavage by the proteolytic enzyme furin, is separated into a 32 amino acid carboxi-terminal biologically active portion (BNP) and a 76 amino acid amino terminal part without biological activity (NT-proBNP) (fig 1).

At present, there are four BNP assays commercially available for routine clinical practice. BNP can be assayed by a rapid fluorescence immunoassay (Biosite Diagnostic), an enzyme immunoassay (Abbott Laboratories), or a chemiluminescent immunoassay (Bayer Healthcare), and NT-proBNP can be measured by an electrochemiluminescent assay (Roche Diagnostics).

ANP and BNP exert their effects through interaction with specific high affinity receptors on the target cells. Three effective receptors have been identified at target sites and kidneys. These receptors, located on cell membranes, although not reflecting their affinity for the different peptides, are termed: natriuretic receptor type A, natriuretic receptor type B, and type C—a clearance receptor.

Most cardiovascular and renal effects of ANP and BNP result from cyclic guanylmonophosphate formation which acts as a second messenger responsible for the cellular physiological responses to natriuretic peptide stimulation.

Natriuretic peptides are cleared from plasma by binding to natriuretic peptide receptors and through proteolysis by peptidases. NT-proBNP has a longer half life than BNP (118 *v* 18 minutes). Renal excretion is currently regarded as the main clearance mechanism of NT-proBNP. Relative concentrations of NT-proBNP and BNP may shift when healthy individuals are compared to heart failure patients. The significance of this shifting is not well understood, but changes in BNP production and shift in the degradation and half life caused by receptor regulation may be the aetiology of this observation.

◀ EFFECTS OF NATRIURETIC PEPTIDES

Natriuretic peptides play a key role in the homeostasis of pressure and volume. Increased secretion of natriuretic peptides reduces blood pressure and plasma volume through coordinate actions in the brain, adrenal gland, kidney, and vasculature. ANP and BNP produce a dose dependent decrease in blood pressure, in part from direct vasodilatation and in part from a reduction in cardiac preload caused by increased venous capacitance and shifting of intravascular volume into the extravascular compartment due to increased permeability of the vascular endothelium and increased hydraulic pressure in the capillary bed. Suppression of the renin–angiotensin–aldosterone system, diuresis and natriuresis are also mechanisms related to the decrease in preload. ANP and BNP lead to a reduction of sympathetic tone through suppression of central sympathetic outflow, dampening of baroreceptors, and suppression of catecholamines from autonomic nerve endings. Anti-mitogenic action of both ANP and BNP has been documented in the cardiovascular and other systems. Renal actions of ANP and BNP lead to natriuresis and diuresis through direct tubular actions and haemodynamic modulation. An increase in glomerular pressure leads to an increase in glomerular filtration (through dilatation of the afferent renal arterioles and constriction of the efferent arterioles) and the relaxation of mesangial cells increases the surface area for filtration. ANP and BNP inhibit angiotensin II stimulated sodium and water transport in proximal convoluted tubules, inhibit water transport in

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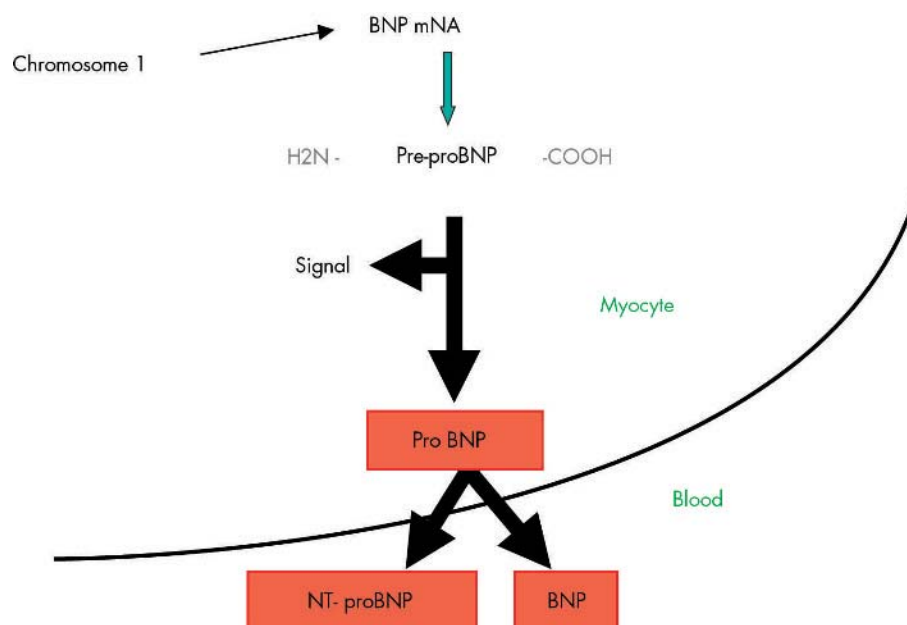
Figure 1 Synthesis and secretion of B-type natriuretic peptide (BNP).

collecting ducts by antagonising vasopressin, and block sodium reabsorption in the inner medullary.[1]

PATHOPHYSIOLOGY

The activation of the cardiac natriuretic peptides is a hallmark of heart failure. The increase in BNP in heart failure is secondary to increased synthesis and release, triggered by wall stretch, ventricular dilation and/or increased pressure, as well as from other local and circulating humoral factors. In chronic heart failure a differential activation of BNP has been described. In an animal model of early left ventricular dysfunction, BNP mRNA and tissue BNP are notably increased in the left atrium but remain low in ventricular myocardium, despite an increase in circulating BNP. In severe heart failure, ventricular mRNA and tissue BNP are also notably increased. This ventricular BNP production contributed significantly to a further increase in circulating BNP. Thus, in contrast to physiologic conditions of early heart failure, severe heart failure is characterised by the activation of ventricular BNP production. This ventricular recruitment of the BNP gene represents a reactivation of the fetal genes programme. Although the plasma concentrations of BNP are significantly increased in heart failure, they are insufficient to produce the biological effects of natriuretic peptides, suggesting that severe heart failure is a state of relative deficiency of natriuretic peptides.[2]

BIOLOGIC DETERMINANTS OF BNP MEASUREMENTS

Blood concentrations of BNP and NT-proBNP increase with age, presumably as a result of left ventricular (LV) stiffness and progressive deterioration of renal function. Uniformly across community cohorts women have higher BNP values than men of the same age strata. Patients with severe lung disease, hypertension, and diabetes may have higher BNP and NT-proBNP concentrations than age matched controls. Patients with impairment of renal function (glomerular filtration rate (GFR) < 60 ml/min) also have higher BNP concentrations than age matched controls. The observation of lower concentrations of BNP in obese people remains unexplained (table 1).

Drugs used in heart failure treatment can modify circulating concentrations of BNP. Diuretics and vasodilators decrease BNP concentrations rapidly (together with falling intracardiac filling pressures); angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and spironolactone also lead to decreases in BNP concentrations. The effects of β blockers on BNP are more complex. On the one hand, because adrenergic stimulation inhibits the release of BNP, initiation of β blockers will slightly increase natriuretic peptide concentrations. On the other hand, long term concentrations of BNP fall because of improvement in neurohumoral ambient, haemodynamic variables and left ventricular function.

BNP TESTING IN CLINICAL PRACTICE

The role of BNP testing is clearly defined for diagnosing patients with suspected heart failure (outpatients with new symptoms and patients with acute dyspnoea) and for assessing the prognosis of heart failure patients. Other promising, although not yet defined, potential uses in routine practice include identification of high risk groups for heart

| Table 1 | B-type natriuretic peptide (BNP) measurement: confounders | |
|---|---|
| **Increase BNP** | **Decrease BNP** |
| Increasing age | Obesity |
| Female sex | Cardioactive drugs: |
| Pulmonary disease | ACE inhibitors |
| Systemic hypertension | Spironolactone |
| Hyperthyroidism | β Blockers (long term) |
| Cushing syndrome | Diuretics |
| Glucocorticoids use | |
| Conn's syndrome | |
| Hepatic cirrhosis with ascites | |
| Renal failure | |
| Paraneoplastic syndrome | |
| Subarachnoid haemorrhage | |

ACE, angiotensin converting enzyme.
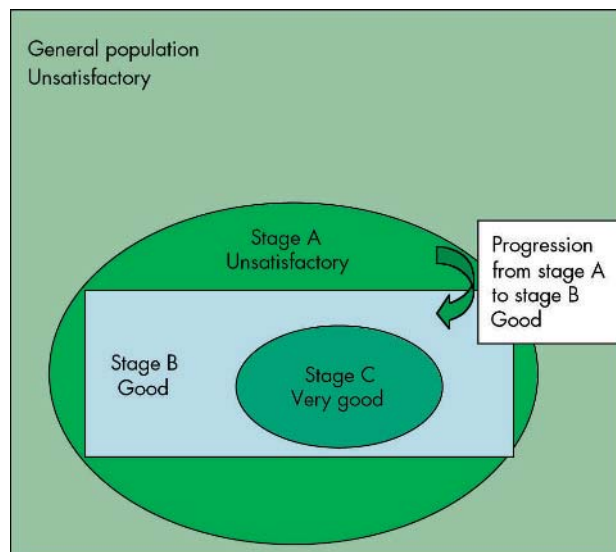
Figure 2 Performance of B-type natriuretic peptide in the identification of left ventricular systolic dysfunction and heart failure.

failure, dynamic risk stratification, and monitoring of heart failure treatment (figs 2 and 3).

DIAGNOSIS

Many years have passed since it was first suggested that natriuretic peptides might aid in the diagnosis, prediction of prognosis, and clinical management of heart failure. Over the years, these concepts have been refined in several ways. The fact that natriuretic peptide plasma concentrations are significantly increased in patients with high left ventricular wall tension led to many studies evaluating the possible role of ANP, NT-proANP, BNP and more recently NT-proBNP as a diagnostic test for heart failure and ventricular dysfunction. In the vast majority of these studies BNP and NT-proBNP proved to be the most accurate natriuretic peptides in the identification of participants with left ventricular systolic dysfunction (LVSD) or heart failure. Many single centre community based epidemiological and hospital cohort studies have now reported on the efficacy of BNP and NT-proBNP in the diagnosis of heart failure and LVSD.

COMMUNITY SCREENING

It is acknowledged that asymptomatic LVSD is a treatable precursor of heart failure. This recognition generated enthusiasm for developing tools for LVSD screening. In the community approximately 75% of systolic dysfunction patients are clinically undetected. Screening for LVSD is, however, challenging as it is present in only 1–2% of the entire population. Until now more than five community based studies have been reported. The overall accuracy (analysed by the area under the ROC curve (AUC)) of BNP and NT-proBNP in the identification of participants with LVSD has varied between the suboptimal value of 0.56 and the clinically relevant value of 0.88. In all of these studies the negative predictive value of BNP and NT-proBNP has been very high (between 93% and 98%), supporting the value of the test in ruling out LVSD. The predictive value of a positive test—that is, a BNP or NT-proBNP above the best cut off value of each study—has been consistently modest (between 15–30%). This means that most participants with high BNP

or NT-proBNP concentrations would be falsely diagnosed as having LVSD. For example, in the Olmsted County cohort, with a low prevalence of LVSD (1.1%), 24% of the population would require an echocardiogram based on raised BNP concentrations and the vast majority of these echocardiograms (96%) would reveal an ejection fraction > 40%. In the North Glasgow cohort (with a prevalence of LVSD of 3.2%) the probability of LVSD was 16% for participants with "high" BNP values. These results show that the performance of BNP and NT-proBNP for the detection of LVSD in the community is fair, mainly because of the low specificity even at cut points yielding very high negative predictive values, compromising any potential usefulness of the test as a screening procedure. Therefore, BNP testing is not appropriate for screening for LVSD in the general population.

Other areas where BNP may have a diagnostic role include the identification of groups at low and high risk of LVSD and the detection of individuals with a range of subclinical cardiovascular disorders with functional or structural cardiac abnormalities. The definition of the high risk LVSD group is probably the cause of the conflicting results reported. Using BNP as a screening test for men and women older than 60 years with previous hypertension and known cardiovascular disease, the potential clinical value is limited, as illustrated by an AUC of 0.65 for men and 0.86 for women. Sub-analysis from the North Glasgow cohort identified a group of high risk individuals based on symptoms, ECG findings, and blood pressure. Using this "high risk" approach, the addition of BNP testing in the clinical assessment programme would reduce the number of echocardiograms needed to identify one participant with systolic dysfunction from 17 to 12. The cost effectiveness of this kind of approach has not been evaluated.[3 4]

The idea of screening for cardiac functional and/or structural abnormalities (stage B heart failure according to the American College of Cardiology/American Heart Association) looks much more interesting and intimately related to the pathophysiology of natriuretic peptides. Data from an Asian population showed that when screening for this purpose, BNP had an overall accuracy of 0.97. The negative predictive value was 99% and the positive predictive value was 44%. Using this broader concept of cardiac abnormalities, BNP screening appears to have a more pertinent role than when used for targeting LVSD. There are also data to suggest that high risk individuals with high BNP concentrations are at risk of developing cardiac structural and functional impairment—that is, BNP testing could be used to identify people who will progress from stage A to stage B heart failure.

The value of BNP for screening high risk groups is not clear. Definition of high risk groups, the target cardiac abnormalities, as well as cost–benefit analysis are necessary before it becomes routine practice.

BNP IN THE DIAGNOSIS OF HEART FAILURE IN SYMPTOMATIC PATIENTS

Symptoms and signs suggestive of heart failure are unspecific and have a low sensitivity to heart failure diagnosis. In primary care more than 70% of patients with suspected heart failure have other disorders accounting for symptoms. Assigning the cause of dyspnoea and exercise intolerance in patients who may have cardiac and non-cardiac disease is a common clinical dilemma. We now have a body of evidence that BNP and NT-proBNP can assist clinicians in the
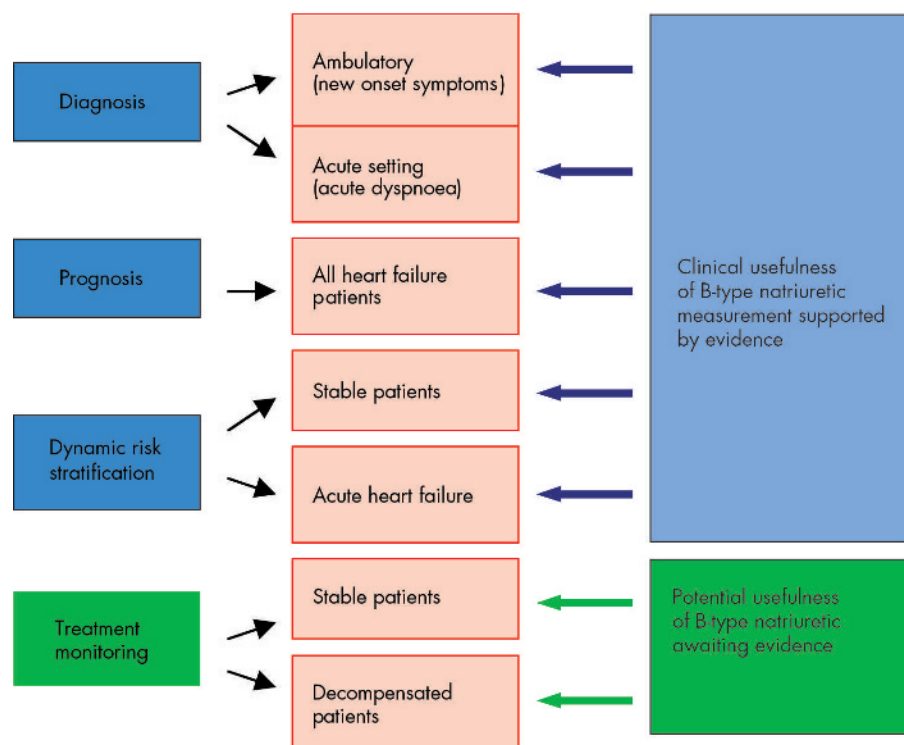
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Figure 3 Use of B-type natriuretic peptide in clinical practice.

diagnosis of heart failure in the ambulatory as well as in the emergency setting.

Potential overall accuracy of BNP in the diagnosis of heart failure in primary care measured by the AUC has been uniformly high across studies. In a landmark study, the Hillingdon heart failure study, of patients with suspected new heart failure, the AUC for BNP was 0.96, with a positive predictive value of 70% and a negative predictive value of 98% at the cut off value of 76 pg/ml.[5] Other trials showed more modest predictive values of a positive result of BNP or NT-proBNP. The very important lesson from these studies is that low BNP or NT-proBNP concentrations during the initial approach to patients with suspected heart failure can confidently exclude heart failure diagnosis. A positive result should lead to investigations in order to detect cardiac functional and structural abnormalities or other conditions associated with raised BNP concentrations (mild to severe chronic obstructive pulmonary disease, renal failure, myocardial ischaemia, atrial fibrillation).

Other groups evaluated the increment in accuracy that NT-proBNP can give to clinicians in the diagnosis of heart failure. It has been shown that general practitioner awareness of NT-proBNP concentrations greatly improves diagnostic accuracy compared to review of clinical records by a cardiologist. These results clearly define a role for NT-proBNP in assisting the diagnosis of heart failure.

Concern over the false negative—that is, heart failure patients with low NT-proBNP concentrations—has been addressed. Heart failure patients with low BNPs are mainly patients with borderline LVSD or are on cardioactive drugs known to lower BNP concentrations.

These observations on the clinical value of BNP and NT-proBNP in the validation of heart failure clinical diagnosis have been mostly based on best cut off points derived from the ROC curves obtained by each study data. In clinical practice physicians rely on normal and abnormal values of a specific test. Using this approach in a subgroup from a multicentred analysis of epidemiological studies of participants with breathlessness, 90% of participants had a plausible cardiovascular cause for high NT-proBNP concentrations, and 4% had renal failure as possible cause of high NT-proBNP.

The rule out value of BNP in the ambulatory setting of patients with suspected new heart failure is well established. In patients with a positive test—that is, high BNP concentrations—a full investigation should be undertaken because cardiovascular, moderate to severe respiratory, or relevant renal abnormalities are very likely to be present. BNP is not a stand alone test—it is of greatest value when it complements clinical judgment along with other available tests.

ACUTE SETTING

Patients presenting with acute dyspnoea frequently pose a challenge to clinicians, the cause being uncertain in up to a third of patients attending emergency departments because of shortness of breath.

Table 2 Diagnosis of acute heart failure based on a score including NT-proBNP, pulmonary x ray, age, and clinical parameters: acute heart failure score (Pride)

Predictor	Points
Elevated NT-proBNP	4
Interstitial oedema on chest x ray	2
Orthopnoea	2
Absence of fever	2
Current loop diuretic use	1
Age >75 years	1
Rales on lung examination	1
Absence of cough	1

A score of >7 has a high predictive accuracy for the diagnosis of acute heart failure.

Preliminary observations suggested that BNP concentrations were higher in patients with dyspnoea caused by heart failure than in dyspnoea resulting from pulmonary disease. More recently, multicentre studies confirmed these observations and provided evidence that determining BNP and NT-proBNP concentrations can help clinicians in the differential diagnosis of acute dyspnoea.[6] The rule-out value of BNP and NT-proBNP in this setting is well documented. Patients with BNP concentrations < 100 pg/ml or NT-proBNP concentrations < 300 pg/ml are very unlikely to have heart failure (negative predictive value 99%). Patients with BNP concentrations > 500 pg/ml or NT-proBNP concentrations > 450 pg/ml (< 50 years of age), 900 pg/ml (50–75 years), and 1800 pg/ml (> 75 years) have a very high probability of having heart failure as the cause of their acute dyspnoea (the clinical judgment must also consider other diagnoses, namely acute coronary syndrome and pulmonary embolism). Patients with BNP concentrations between 100–500 pg/ml or NT-proBNP concentrations between 300 pg/ml and 450, 900, and 1500 pg/ml, respectively, according to age, have several other diagnostic possibilities that need to be considered. Across the trials, in the acute setting BNP proved superior to clinical judgment, but the best performance has been achieved by combining BNP results with clinical judgment. A score using clinical parameters together with NT-proBNP has been developed and tested in an independent population, and has proven to have a very high predictive value for the diagnosis of acute heart failure (table 2). Diagnostic algorithms incorporating BNP determination have been developed in order to alert clinicians to the potential usefulness of BNP measurement and also to call attention to alternatives.

BNP testing improves the ability to diagnose and exclude heart failure in patients with acute dyspnoea. Combination of a strategy based on BNP determination and clinical assessment is the ideal approach to optimise early diagnosis and intervention.[7 8]

Decision cut-points for heart failure diagnosis, based on consensus between expert opinions and manufacturers, are summarised in table 3. Cut-points are not yet clearly defined and more work is required to optimise them. Local centres should be audited before deciding on cut-points in their own populations, in consultation with the local biochemical laboratory. Assays characteristics must also be considered.

BNP FOR ESTIMATING HEART FAILURE PROGNOSIS

BNP is a powerful prognosis index in the heart failure setting. Higher concentrations of BNP are associated with increased cardiovascular and all cause mortality, independently of age,

Clinical usefulness of BNP measurement: key points

▶ B-type natriuretic peptide (BNP) can be measured in serum and plasma as a biologically active portion BNP and as an amino terminal portion NT-proBNP

▶ Ventricular wall stretch is the major determinant of increased BNP concentrations in heart failure patients

▶ BNP has a very high negative predictive value for the identification of persons with left ventricular systolic dysfunction and heart failure

▶ The prognostic power of BNP is well established in heart failure patients; serial determination of BNP can improve prognostic information in compensated and decompensated heart failure patients

▶ Treatment titration aimed at lowering BNP is promising and will probably modify the therapeutic approach to heart failure patients in the near future

New York Heart Association (NYHA) class, and ejection fraction. The prognostic usefulness of BNP is well documented in the whole spectrum of heart failure severity and is observed regardless of heart failure treatment. Raised concentrations of BNP are also independently associated with sudden cardiac death. BNP is higher in patients with more severe symptoms and those with more severe cardiac impairment. However, the clinical impact of BNP determination as a prognostic index is still controversial. Risk stratification based on BNP has been suggested mainly in the selection of patients needing cardiac transplantation and in the identification of patients at low risk of adverse events suitable for conservative approaches.

DYNAMIC RISK STRATIFICATION

There is increased enthusiasm in the utility of serial BNP measurement for risk stratification. Data from outpatients show that serial determination of BNP can improve the prognostic determination in heart failure patients. The identification of patients at high risk of adverse outcomes is suggested as a way for more aggressive intervention and close follow up, but clinical evidence supporting this suggestion is still lacking.

In decompensated heart failure serial determinations of BNP have been shown to be associated with outcomes in observational studies. Patients not achieving significant decreases in NT-proBNP concentrations (30% decreases) have a very high incidence (80%) of hospital readmission or death in a six month period. These observations led to the consideration that BNP may be used to help clinicians arrive at the discharge decision. A randomised controlled trial of

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Table 3 Proposed cut-off for ruling in and ruling out heart failure

	Heart failure in ambulatory setting	Acute dyspnoea
Rule-out heart failure		
NT-proBNP	<125 pg/ml <75 years <450 pg/ml ≥75 years	NT-proBNP <300 pg/ml
BNP	<70 pg/ml	BNP <100 pg/ml GFR <60 ml/min BNP 200 pg/ml
Rule-in heart failure		
NT-proBNP		Age >75: NT-proBNP >1800 pg/ml Age 50–75: NT-proBNP >900 pg/ml Age <50: NT-proBNP >450 pg/ml
BNP		>500 pg/ml

BNP, B-type natriuretic peptide; GFR, glomerular filtration rate.

treatment modification and discharge time according to change in BNP from admission to the point where clinical compensation is thought to have been achieved is necessary to confirm this suggestion.[9]

BNP FOR TITRATING HEART FAILURE TREATMENT

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BNP testing can help physicians to make clinical decisions in heart failure patients, although much work is necessary in this emerging field before it can be used in clinical practice. BNP concentrations are known to fall with treatment for heart failure. The concept is that the decision to titrate heart failure treatment or to use more aggressive strategies might be based not only on "state of the art" knowledge but also on BNP concentrations. Because BNP decreases in patients improving clinically, treatment of heart failure patients with vasodilators titrated to decrease BNP to normal ranges is feasible. There is some evidence for the possible benefit of an NT-proBNP guided treatment approach.[10] A pilot randomised study found fewer total cardiovascular events in the group randomised to NT-proBNP guided treatment compared to a similar group of patients whose treatment was guided by commonly used clinical variables. Larger studies are now underway in order to answer important questions related to this issue. Can BNP be used as an instrument to individualise treatment in heart failure? What is the best BNP target concentration?

However, there are still concerns on the role of BNP in treatment monitoring. BNP rises as renal function declines, so reduction of BNP based on diuretics may result in worsening renal function and subsequent increases in BNP concentrations. In addition, the knowledge of biological variability of BNP in heart failure patients is needed for clinicians to be able to interpret BNP changes over time.

FUTURE OF BNP TESTING IN HEART FAILURE

Several fields are currently under investigation: cost effective strategies for selecting persons at high risk of LVSD for further cardiac investigations; and diagnosis of diastolic heart failure (there may be a potential for BNP testing as suggested by preliminary results). Work in progress in dynamic risk stratification based on serial BNP will clarify its value in the identification of patients at high risk warranting aggressive treatment, and of patients without significant neurohumoral activation with good prognosis.

The more exciting perspective of BNP testing is undoubtedly in monitoring treatments in heart failure patients.

Studies designed to test if intensification of treatment guided by BNP determination improves outcomes compared to "state of art" therapy are ongoing and will hopefully give important insights into the individualised management of heart failure.

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